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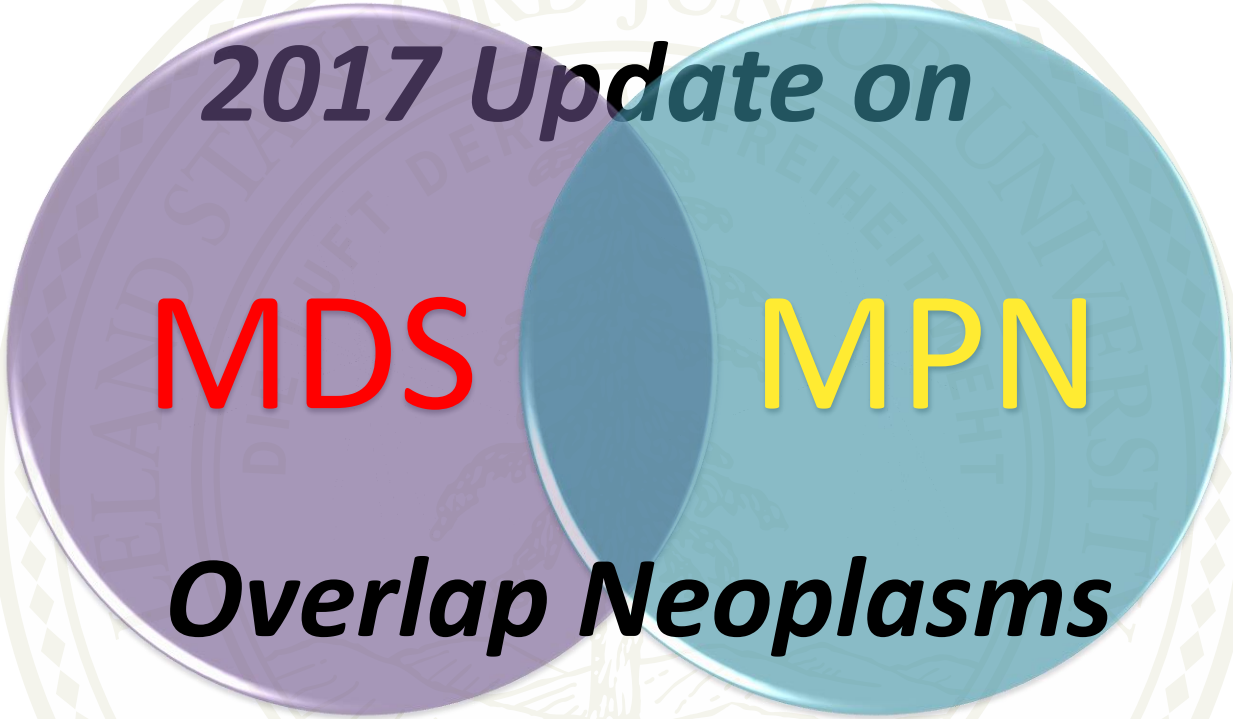
2017 Update on



Overlap Neoplasms

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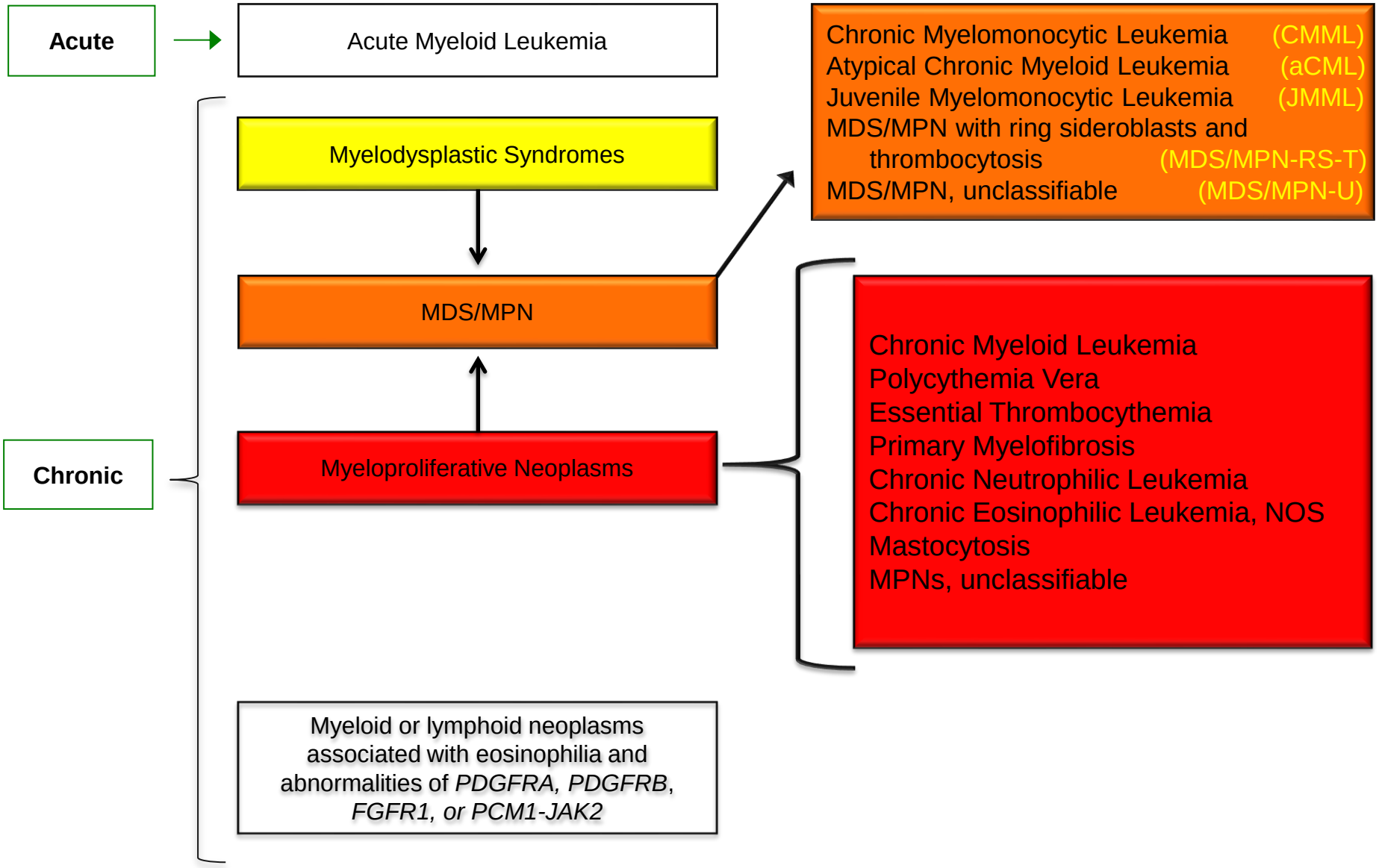
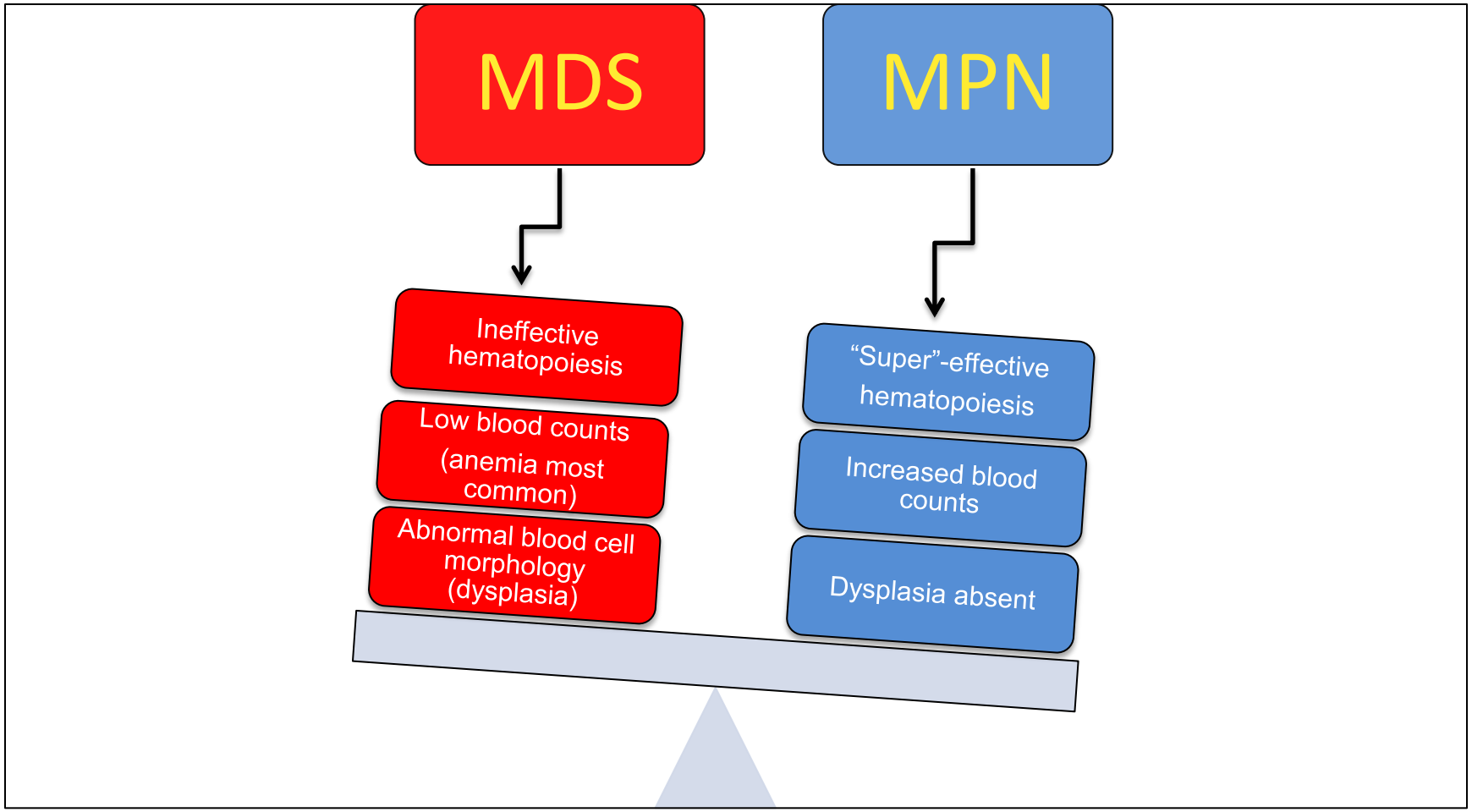
MAYO MPN PATIENT CONFERENCE: FEBRUARY 26, 2017

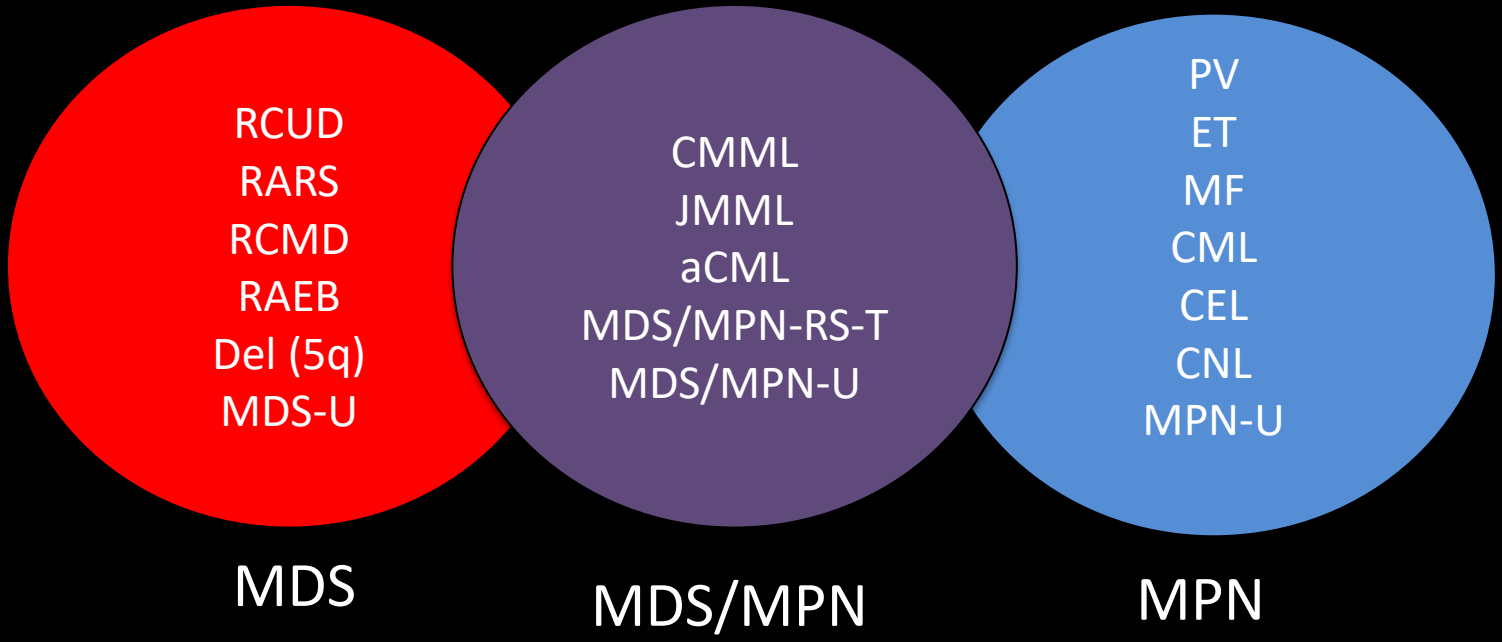
2016 WHO Classification Scheme for Myeloid Neoplasms

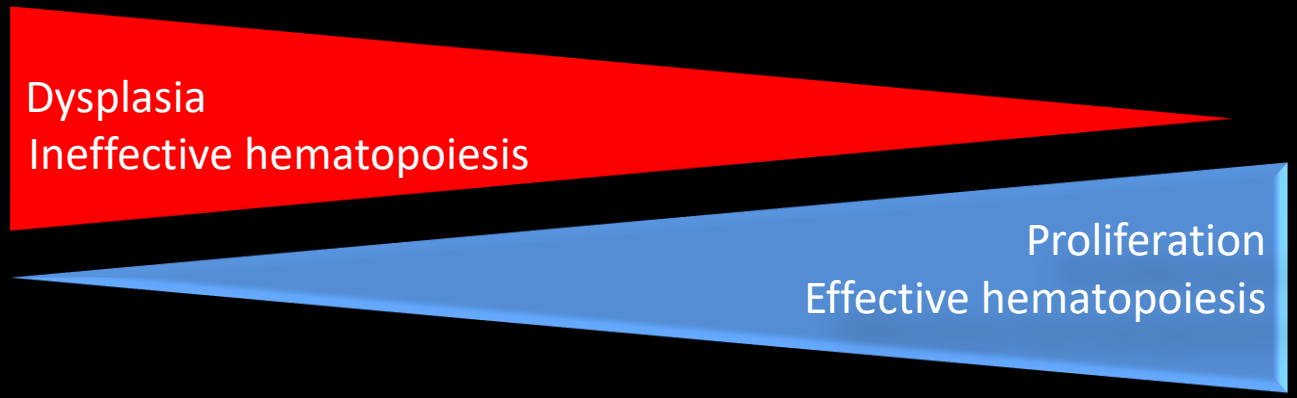


Features of MDS and MPN



MDS / MPN:
An Overlap Neoplasm





Some Things Shouldn't Overlap

2016 World Health Organization Classification of MDS

Subtype	Blood	Bone marrow
MDS with single lineage dysplasia (MDS-SLD)[3]	Single or bicytopenia	Dysplasia in ≥10% of one cell line, <5% blasts
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors w/ring sideroblasts, or ≥5% ring sideroblasts if *SF3B1* mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenia(s), <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2%–4% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5%–19% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ±1% blasts on at least 2 occasions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts
Refractory cytopenia of childhood	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts
MDS with excess blasts in transformation (MDS-EB-T)[2]	Cytopenias, 5%–19% blasts	Multilineage dysplasia, 20%–29% blasts, ± Auer rods

MDS: Revised International Prognostic Scoring System (IPSS-R)

caculate risk score

cytogenetic risk group

very good	0	del(11q), -Y
good	1	normal, del(20), del(5q) alone or with other anomaly, del(12p)
intermediate	2	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones
poor	3	der(3q), -7, double with del(7q), complex with 3 abnormalities
very poor	4	complex with > 3 abnormalities

bone marrow blast %

≤ 2%	0
> 2% - < 5%	1
5% - 10%	2
> 10%	3

hemoglobin (g/dL)

≥ 10	0
8 - < 10	1
< 8	1.5

platelet count (x 10^9/L)

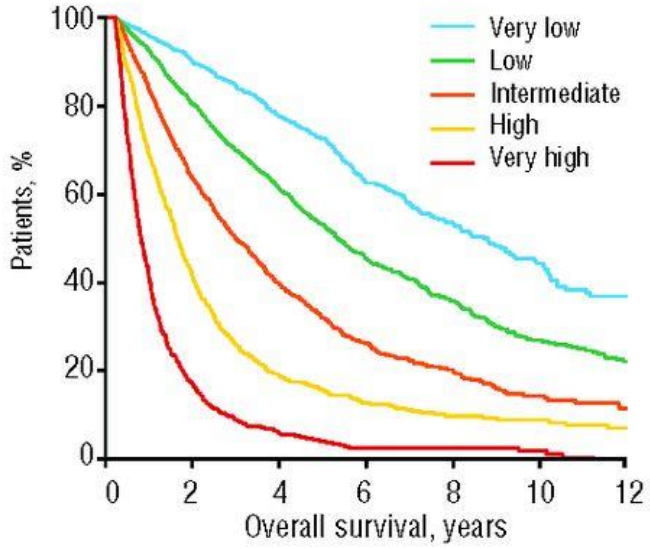
≥ 100	0
50 - < 100	0.5
< 50	1

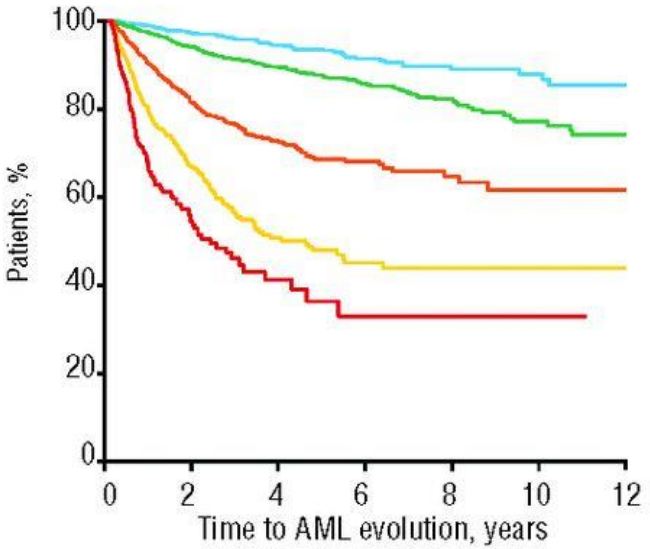
absolute neutrophil count (x 10^9/L)

≥ 0.8	0
< 0.8	0.5

assign IPSS-R risk group

total score	% of patients	median survival, years	time to 25% with AML, years	IPSS-R risk group
≤ 1.5	19%	8.8	not reached	very low
> 1.5 - 3	38%	5.3	10.8	low
> 3 - 4.5	20%	3	3.2	intermediate
> 4.5 - 6	13%	1.6	1.4	high
> 6	10%	0.8	0.73	very high





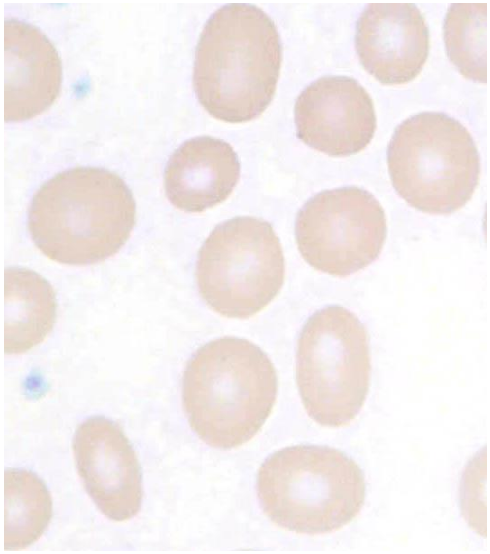
2016 World Health Organization Classification of MDS/MPN

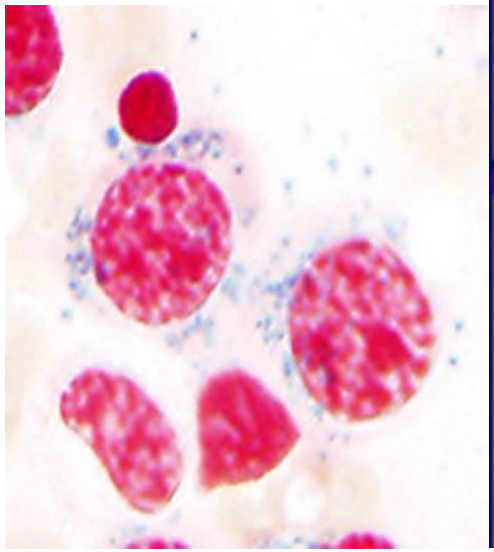
	Blood	Marrow
CMML-0	>1000 monocytes/ul <2% blasts	Dysplasia in ≥1 cell line, <5% blasts
CMML-1	>1000 monocytes/ul 2-4% blasts	Dysplasia in ≥1 cell line, 5-9% blasts

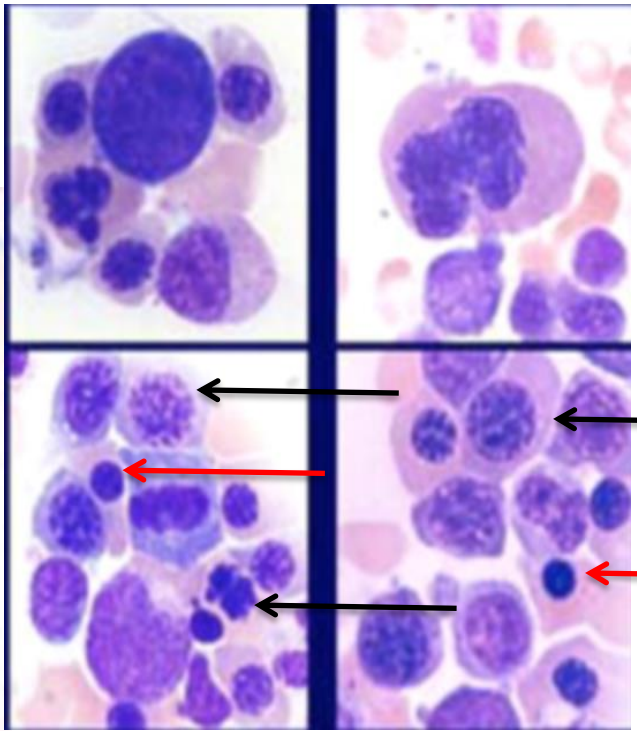
What is ‘Dysplasia’?

Red Blood Cell (Erythroid) Dysplasia (Dyserythropoiesis)

Blood	Marrow iron stain	Red blood cell precursors in the marrow
Macro-ovalocytes	Ring sideroblasts	

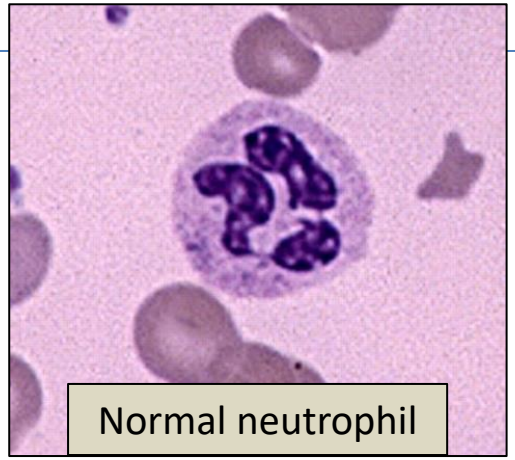


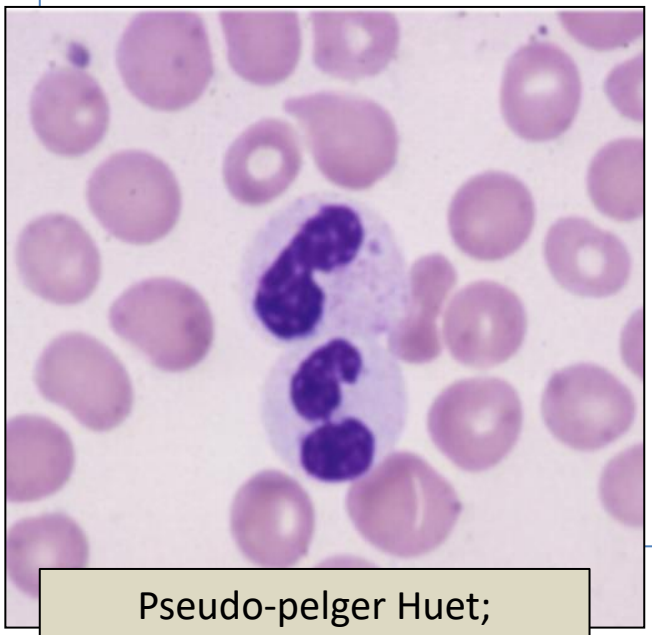


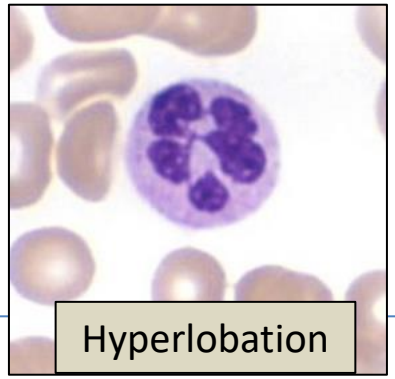


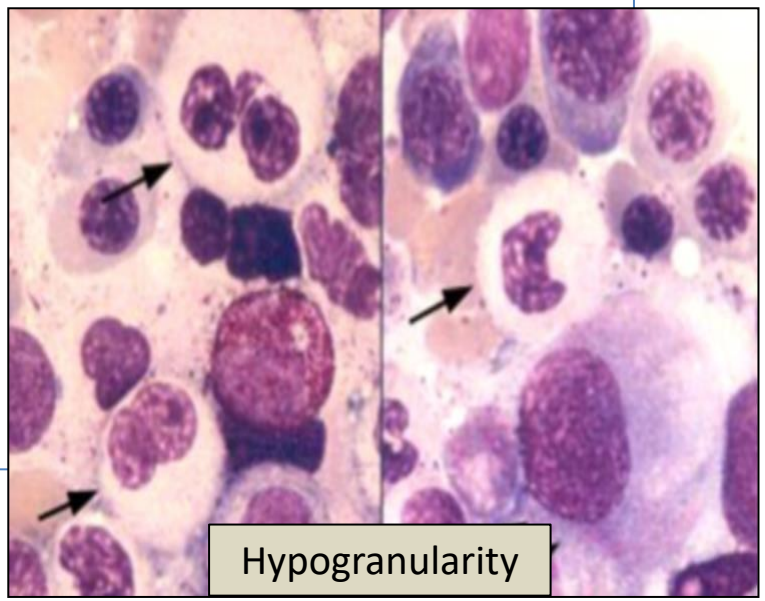
White Blood cell dysplasia (Dysgranulopoiesis)

- Hypogranularity
- Hypolobation
- Hyperlobation
- Pseudo-Pelger Huet cells


Normal neutrophil

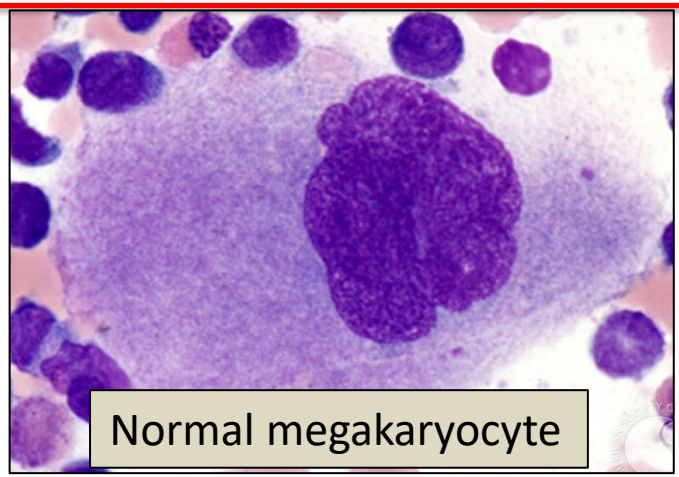

Pseudo-pelger Huet; hypolobation


Hyperlobation

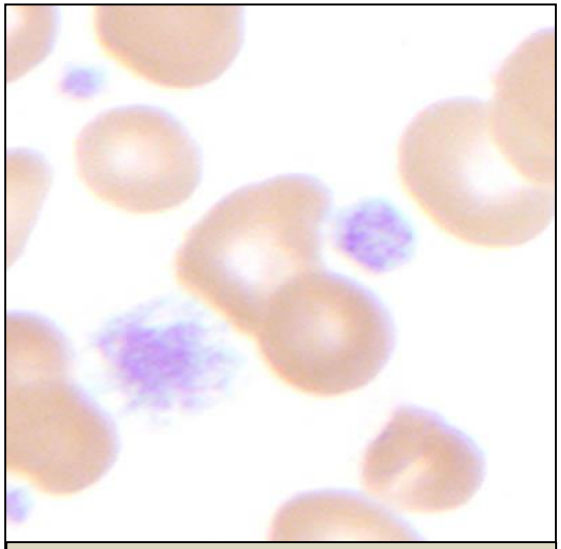

Hypogranularity

Megakaryocyte/platelet dysplasia (Dysmegakaryopoiesis)

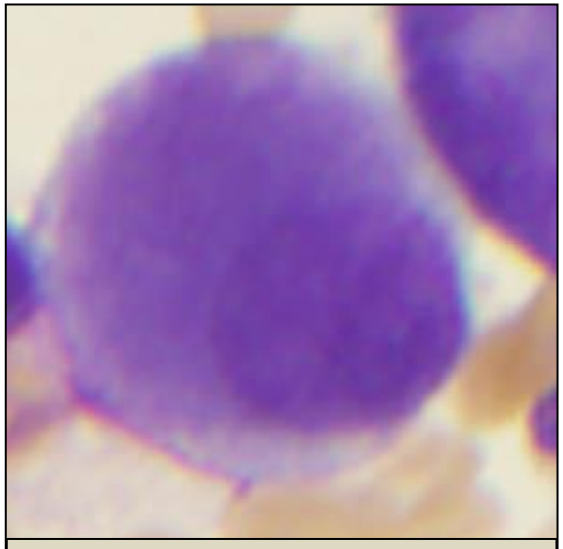
- Micro/dwarf megakaryocytes
- Hypolobation; separate nucler lobes
- Platelets - giant, bizarre, hypogranular



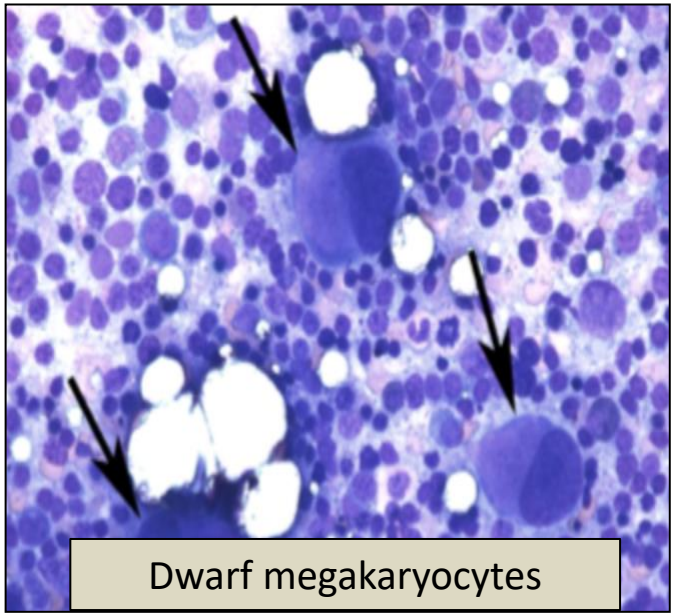
Normal megakaryocyte



Large, hypogranular platelets

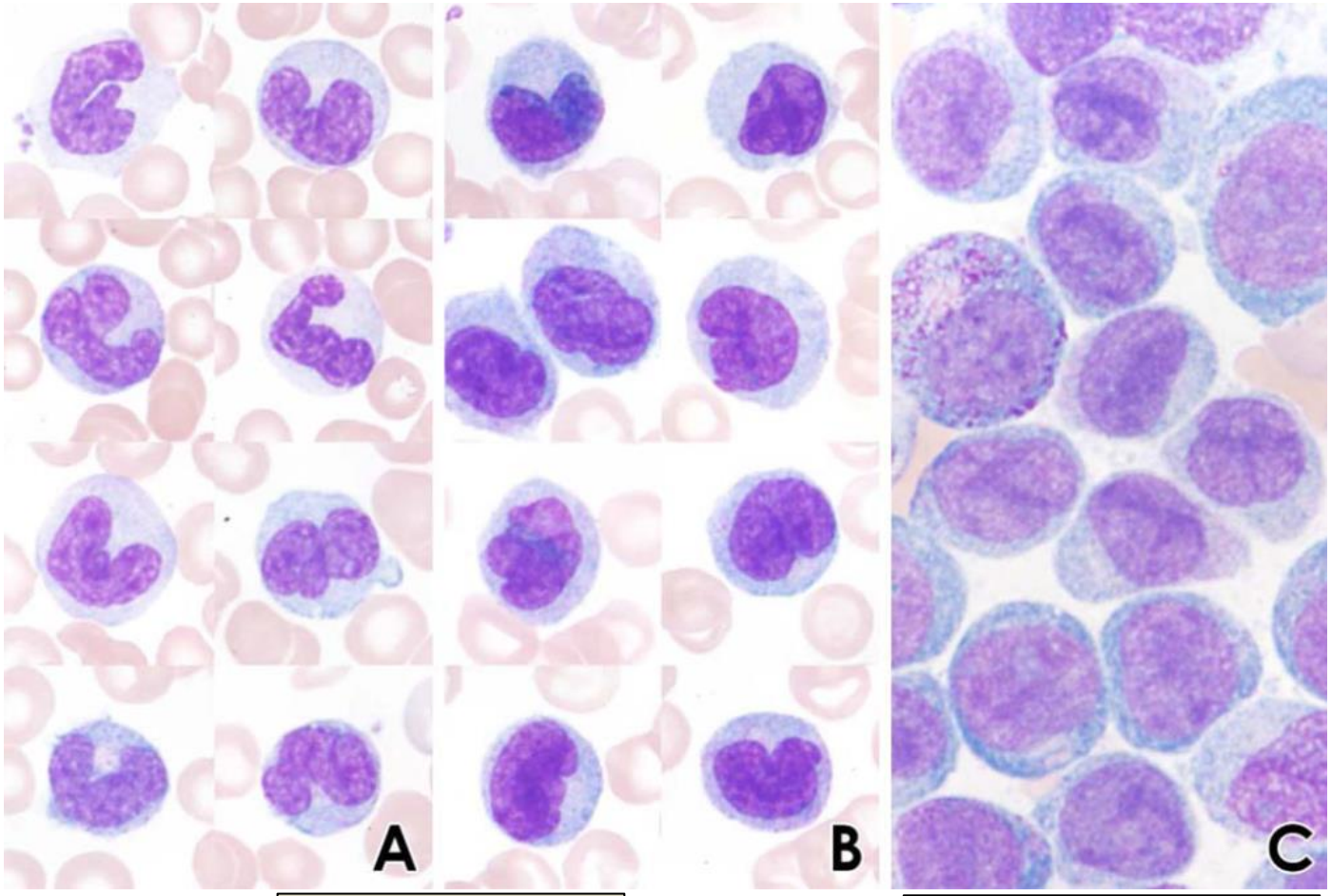


Hypolobated megakaryocyte



Dwarf megakaryocytes

Monocytes in CMML

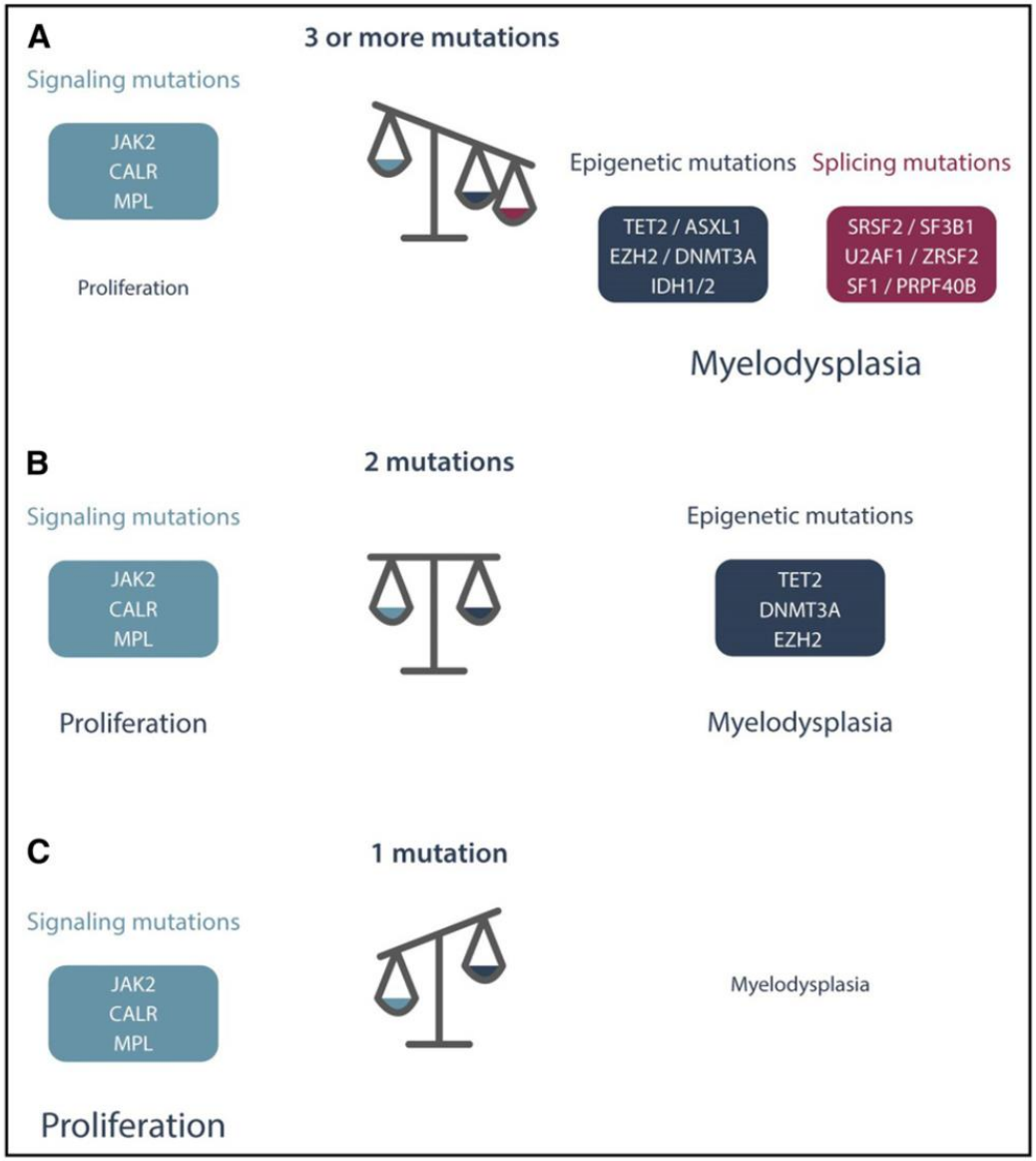


Peripheral Blood

Bone Marrow Aspirate

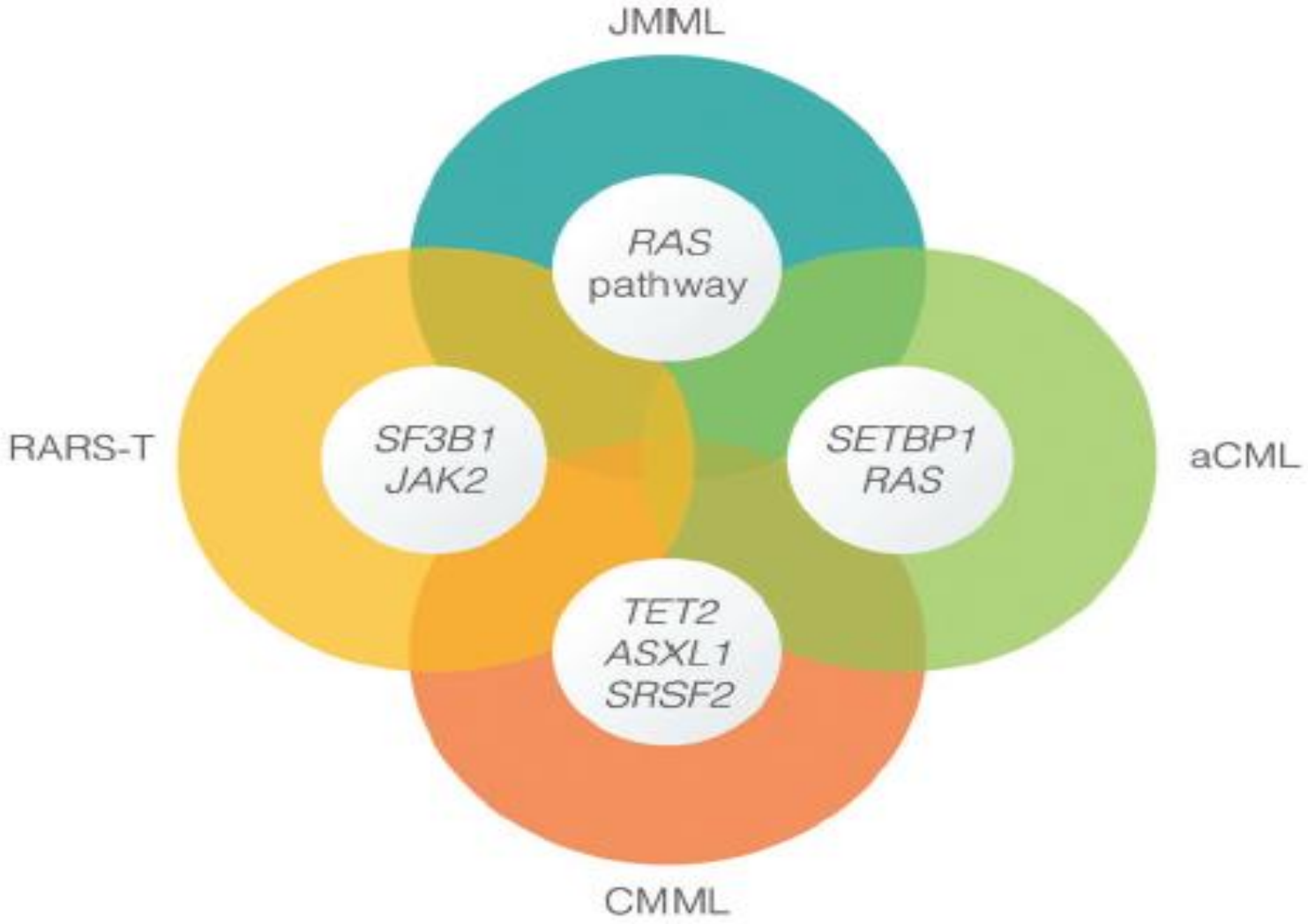
Mutations in MDS/MPN

How Certain Mutations May 'Tip the Scales' Toward MPN vs. MDS



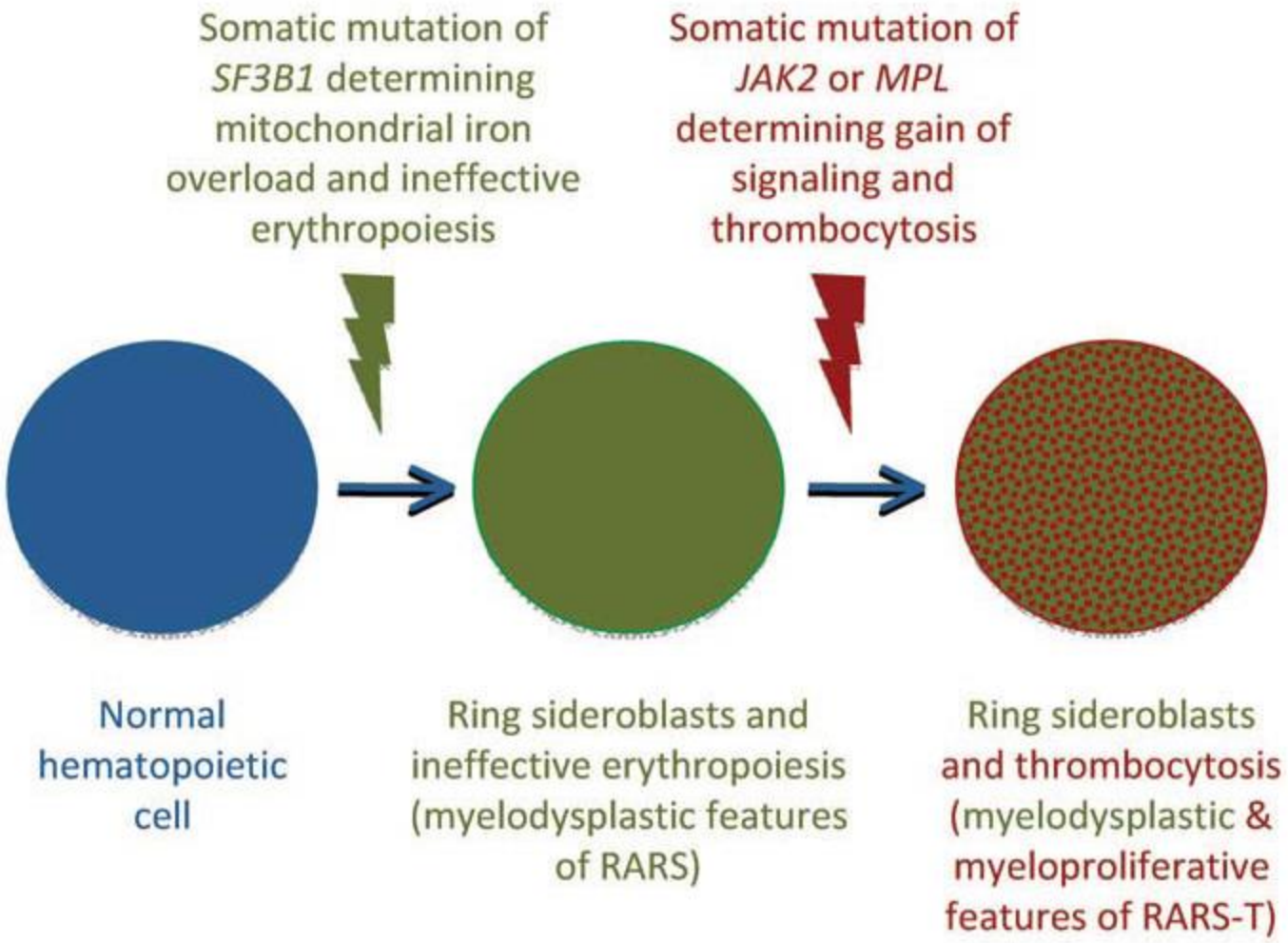
Vainchenker Kralovics, *Blood*, 2017

Mutational Landscape of MDS/MPN



Mughal *et al*, *Haematologica*, 2015

MDS/MPN-RS-T (RARS-T): Mutational Pathogenesis



From Cazzola *et al*, *Hematology Am Soc Hematol Educ Program*, 2011

Prognosis in MDS/MPN

Prognostic Factors in CMML

Factor	Outcome and hazard ratio (HR) (*P* value)	Comment
BM blasts $\geq$ 10%	Overall survival, HR 1.8 ($P < .0001$)	This parameter separates CMML-1 (BM blasts $<$ 10%) from CMML-2 (BM blasts 10%-19%).
WBC count $\geq 13 \times 10^9$/L	Overall survival, HR 2.6 ($P < .0001$) and progression to AML, HR 2.9 ($P < .0001$)	This parameter separates myelodysplastic-like CMML (WBC $< 13 \times 10^9$/L) from myeloproliferative-like CMML (WBC $\geq 13 \times 10^9$/L).
Hemoglobin level $<$ 10 g/dL	Overall survival, HR 1.5 ($P < .0001$)	Severe anemia may reflect clonally advanced myeloid neoplasm.
CMML-specific cytogenetic risk†	Overall survival, HR 1.7 ($P < .0001$)	Abnormalities of chromosome 7 and complex karyotype represent negative prognostic factors in myeloid neoplasms.
Platelet count $< 100 \times 10^9$/L	Overall survival, HR 2.1 ($P < .0001$)	Thrombocytopenia may reflect clonally advanced myeloid neoplasm.

From Cazzola *et al*, *Hematology Am Soc Hematol Educ Program*, 2011

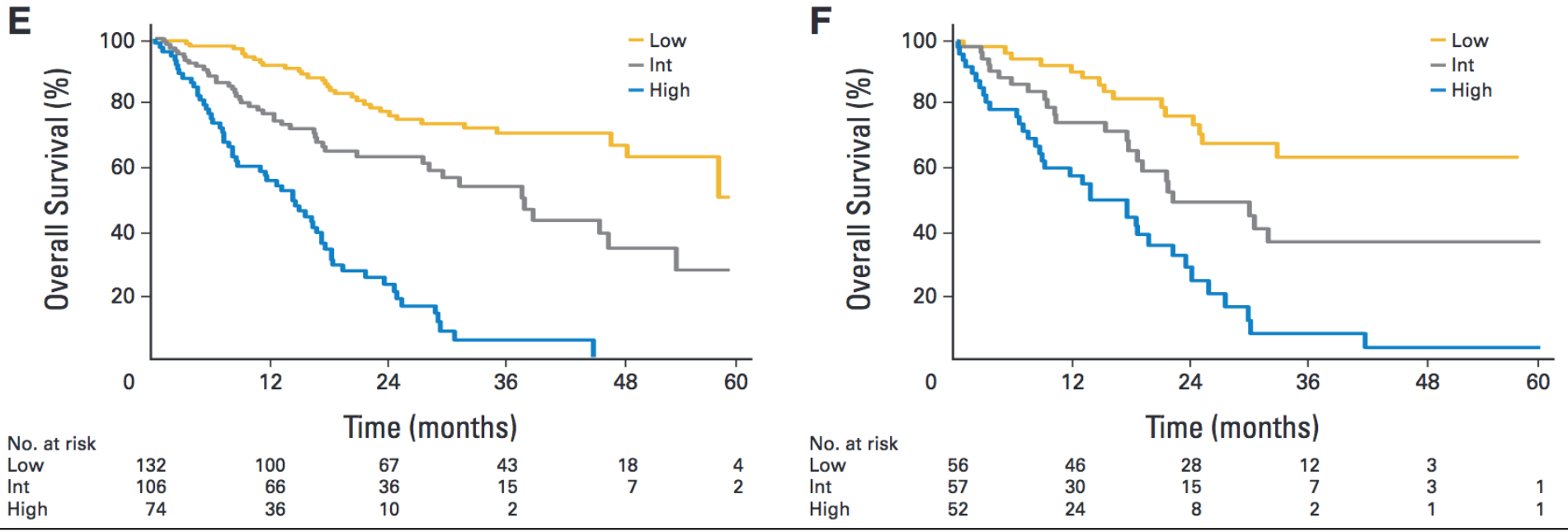
CMML Prognostic Model: Bone Marrow Blast % and WBC Count

Subtype	Overall Survival (Months) n=386	Overall Survival (Months) CMML/MDS n=204	Overall Survival (Months) CMML/MPN n=182	P-value	AML Progression at 2 years
CMML-0 <5% blasts n=101	31	**48**	**17**	.03	**7%**
CMML-I 5-9% blasts n= 204	19	**29**	**15**	.008	**18%**
CMML-2 10-19% blasts n=81	13	**17**	**10**	.09	**36%**

*WBC ≤ vs >13,000 (CMML/MDS vs CMML/MPN)

Schuler et al, Leuk Res 2015

CMML Prognostic Scoring System

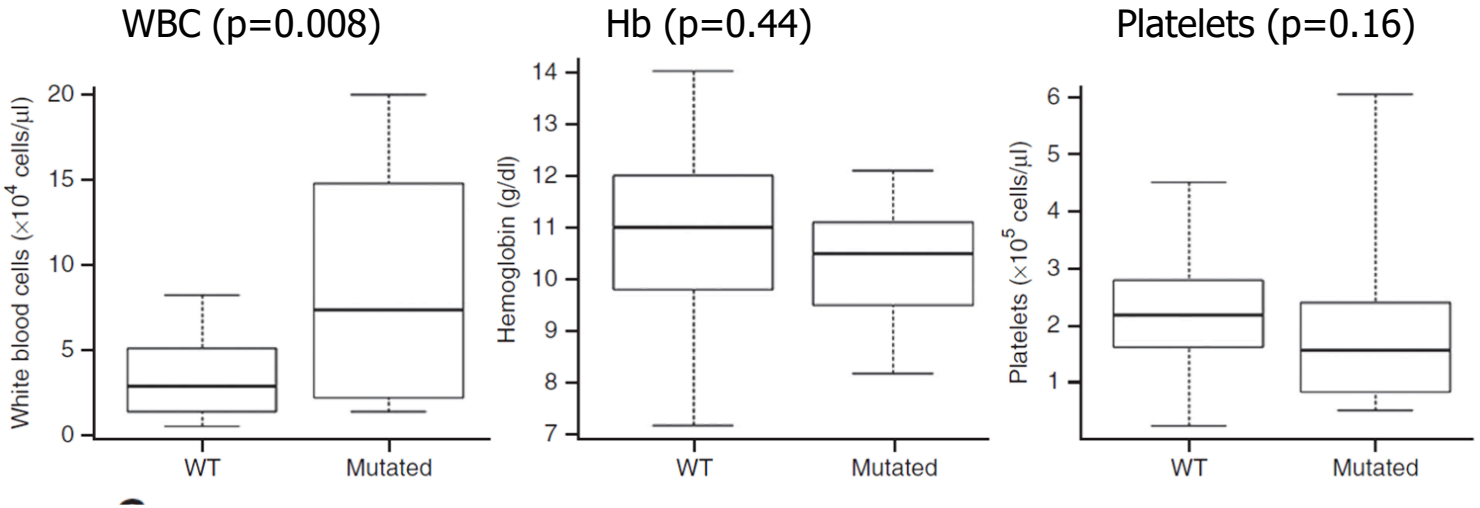


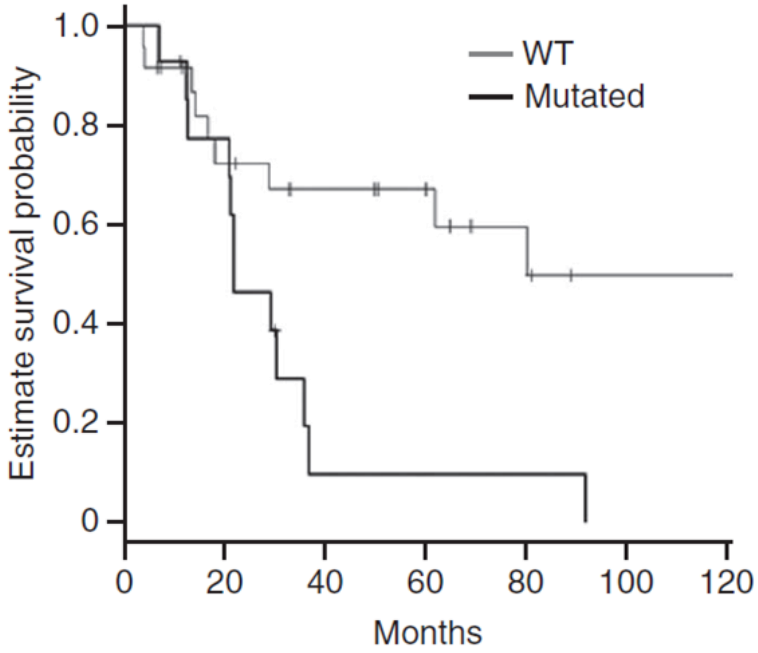
	Absence	Presence
Leucocytosis (>15)	0	3
Age (>65)	0	2
Anemia	0	2
Thrombocytopenia (<100)	0	2
ASXL1 mutation	0	2

Low < 4
Intermediate 4-8
High >8

Itsykson *et al*, *J Clin Oncol*, 2013

SETBP1 Mutation in Atypical CML





SETBP1- = 77 months
SETBP1+ = 22 months

p=0.01, HR=2,27

Piazza R. *et al*, Nat Genetics 2013

Atypical CML: Disease Course

- The largest series of WHO-defined aCML: 55 cases from an Italian cohort.[1]
- **Overall median survival:** 25 months compared with survivals ranging from 14 to 30 months from 3 smaller studies.[2-4]
- **Transformation to AML** occurred in 22 patients (40%), with a median time from diagnosis of 18 months in the Italian study.[1]
- **Predictors of shorter survival:** older age (>65 years), female gender, WBC count (>50x10^9/L), and presence of immature circulating cells.[1]

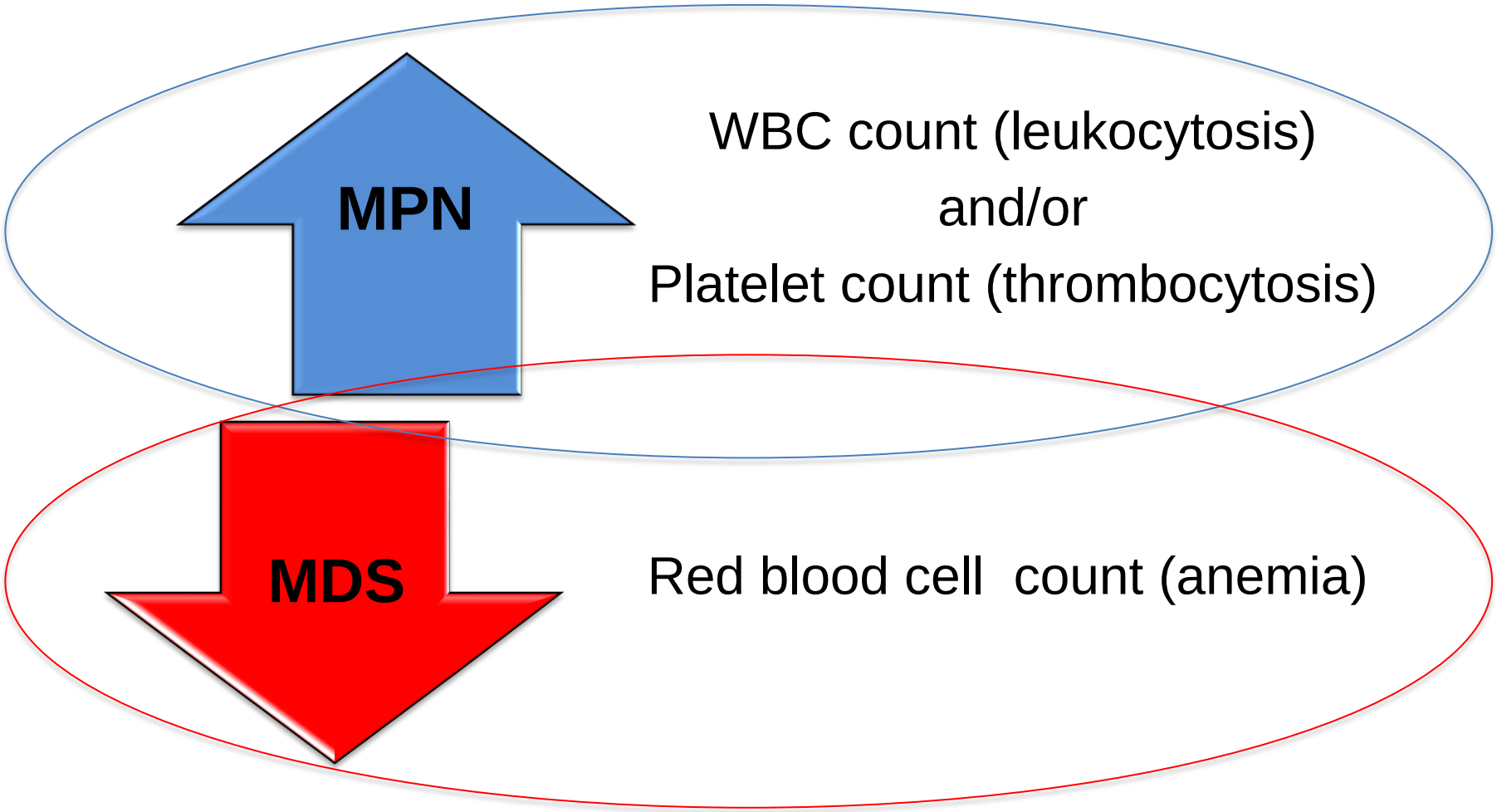
[1] Breccia *et al*, *Haematologica,* 2006
[2] Kurzrock *et al*, *J Clin Oncol,* 2001
[3] Martiat *et al*, *Blood*, 1991
[4] Hernandez *et al*, *Ann Oncol,* 2000

Clinical Management

Goals of Therapy in MDS/MPN

- Cure
- Reduction of symptoms / splenomegaly
- Improvement of blood counts
- Cytogenetic / molecular remission
- Avoidance of disease progression / AML

Common Clinical Issues in MDS/MPN



Case

- **A 68 year-old man presents with a 6-month history of progressive fatigue. His CBC shows the following:**

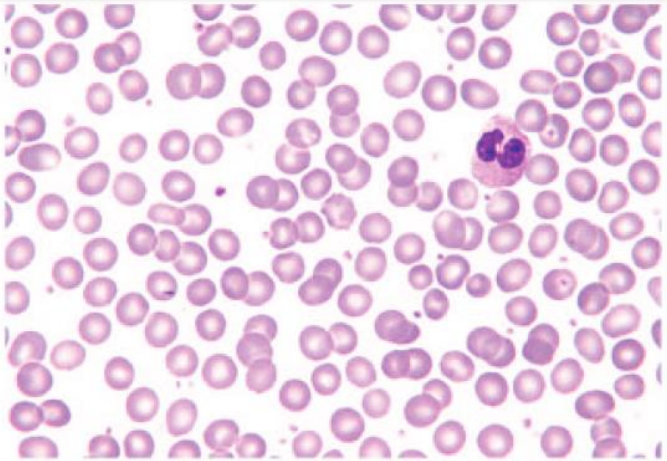
- **White blood cell count:** 5,800/ul (normal: 4,000-11,000/ul)
- **Hemoglobin/hematocrit:** 8.4 g/dL / 27% (normal ~ 15 g/dL; 45%)
- **Platelets:** 620,000/ul (normal: 150,000-400,000/ul)

- **A peripheral blood smear is reviewed and a bone marrow biopsy is performed.**

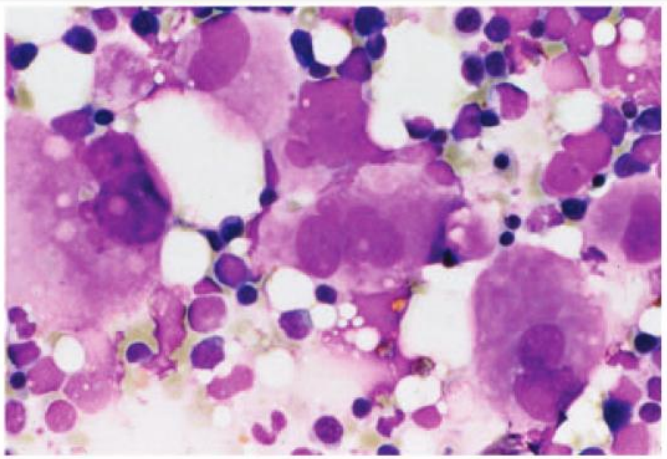
Case (continued)

Peripheral blood:

Increased platelets & dysplastic neutrophil



A



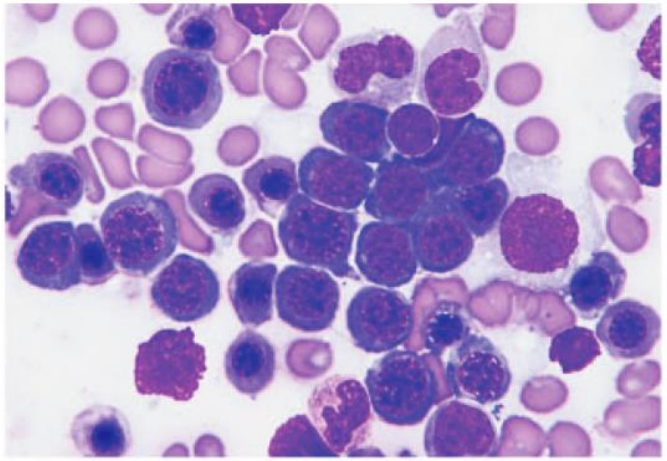
B

BM aspirate:

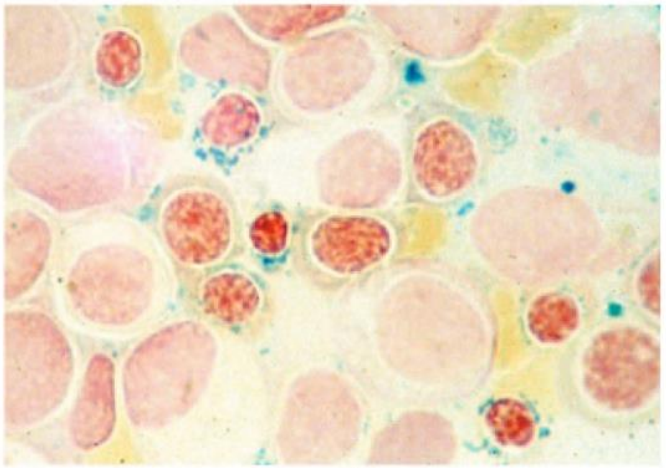
increased clustered megas

BM aspirate:

dysplastic erythroids



C



D

BM aspirate:

ring sideroblasts

Cytogenetics: normal
Myeloid mutation panel: ***SF3B1*** & ***JAK2*** **V617F**

Diagnosis:
MDS/MPN-RS-T

From Cazzola *et al*, *Hematology Am Soc Hematol Educ Program*, 2011

Conventional Medications for MDS/MPN

Summary of Phase I/II Trials of Hypomethylating Therapy in CMML

- **Overall response rate:** 25-70% (usually ~30-40%)[1]
- **Complete remission rate:** 10-58%
- **Overall Survival (OS):** 12-37 months

Prognostic factors for OS in pts treated with azacitidine

- **Worse OS**: BM blasts >10% and WBC >13 x 10^9/L [2]
- **Better OS:** Absolute monocyte count <10 x 10^9/L and PB blasts <5% [3]

[1] Patnaik and Tefferi, *Am J Hematol*, 2016
[2] Ades *et al*, *Leuk Res*, 2013
[3] Fianchi, *et al*, *Leuk Lymphoma*, 2013

Transplantation in CMML

- No randomized trials
- Increasing use of reduced intensity conditioning
  - Other donor sources: haploidentical; double umbilical cord units

- **FHCRC** (n=85)[1]
  - 10-yr overall and relapse-free survival: 40% an 38%, respectively
  - Increasing age, higher SCT co-morbidity index, and poor-risk cytogenetics were associated with increased mortality and reduced relapse-free survival

- **EBMT** (n=513; 95 pts with sAML)[2]
  - 4-year overall and relapse-free survival: 33% and 27%, respectively
  - In multivariate analysis, the only significant prognostic factor for survival was the presence of a complete remission at time of transplantation

[1] Eissa H et al, Biol Blood Bone Marrow Transplant, 2011
[2] Symeonidis *et al*, Br J Haematol, 2015

Targeted Therapy Considerations

Mutation	Therapy	Example
JAK2 V617F	JAK inhibitor	Ruxolitinib
CSF3R T618I	JAK inhibitor	Ruxolitinib
RAS pathway (e.g. *PTPN11, RAS, CBL, NF1*)	MEK inhibitor	Trametinib
SF3B1	TGF-B ligand trap	Luspatercept
Other splicing gene mutations (e.g. *SRSF2*)	Splicing modulator	H3B-8800
IDH 1/2	IDH 1/2 inhibitor	Enasidinib

Consensus Response Criteria for MDS/MPN

Perspectives

An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults

Michael R. Savona,[1] Luca Malcovati,[2] Rami Komrokji,[3] Ramon V. Tiu,[4] Tariq I. Mughal,[5] Attilio Orazi,[6] Jean-Jacques Kiladjian,[7] Eric Padron,[3] Eric Solary,[8] Raoul Tibes,[9] Raphael Itzykson,[7] Mario Cazzola,[2] Ruben Mesa,[9] Jaroslaw Maciejewski,[4] Pierre Fenaux,[7] Guillermo Garcia-Manero,[10] Aaron Gerds,[4] Guillermo Sanz,[11] Charlotte M. Niemeyer,[12] Francisco Cervantes,[13] Ulrich Germing,[14] Nicholas C. P. Cross,[15] and Alan F. List,[3] on behalf of the MDS/MPN International Working Group

[1]Vanderbilt-Ingram Cancer Center/Vanderbilt University Medical Center, TN; [2]University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [3]H. Lee Moffitt Cancer Center, Tampa, FL; [4]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [5]Tufts University Medical Center, Boston, MA; [6]Weill Cornell Medical College, New York, NY; [7]Hôpital Saint-Louis, Assistance Publique – Hôpitaux de Paris, Université Paris Diderot, Paris, France; [8]Institut Gustave Roussy, Villejuif, France; [9]Mayo Clinic Cancer Center, Scottsdale, AZ; [10]MD Anderson Cancer Center, Houston, TX; [11]Hospital Universitario y Politecnico La Fe, Valencia, Spain; [12]University of Freiburg, Germany; [13]The August Pi i Sunyer Biomedical Research Institute, University of Barcelona, Barcelona, Spain; [14]University of Düsseldorf, Düsseldorf, Germany; and [15]University of Southampton and Wessex Regional Genetics Laboratory, Salisbury, United Kingdom

Savona *et al*, *Blood*, 2015

MDS/MPN: Summary

- Clinical, laboratory, pathology, and genetic features are used to diagnose MDS/MPN and its subtypes
- The combination of increased WBC and/or platelet counts with anemia can make treatment decisions challenging; hypomethylating agents are commonly employed
- For younger patients with higher-risk disease and an acceptable co-morbidity index, allogeneic HSCT is the preferred treatment
- Searching for actionable mutations may provide opportunities for targeted therapy; accrual in clinical trials is highly recommended for these rare diseases

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Ruben Mesa
John Camoriano

Community of MPN Investigators

Our Patients & Their Caregivers